Plasma ANP and Renin-Angiotensin-Aldosterone System as New Parameters Describing the Hemodynamics of the Circulatory System after Implantation of Stented or Stentless Aortic Valves

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Background and aim of the study: **Aortic valve replacement (AVR) in patients with a small aortic root involves the occurrence of patient-prosthesis mismatch (PPM). Recent reports have shown that a reduced effective orifice area index (EOAI) may not be the sole factor responsible for this complication. The study aim was to analyze the activity of atrial natriuretic peptide (ANP)/renin-angiotensin-aldosterone (RAA) after implantation of stented or stentless valves.**

Methods: **Between 2001 and 2003, a total of 30 patients operated on at the authors' institution received either a stentless Freestyle® bioprosthesis (group A; n = 15) or a stented Mosaic® bioprosthesis (group B; n = 15). The demographics of both groups were similar, and all patients underwent echocardiography preoperatively, and at one, six and 12 months postoperatively. The activity of the RAA system and plasma ANP level were measured in all patients preoperatively and at one and six months postoperatively.**

Results: **At one month after AVR, statistically significant inter-group differences were noted in plasma renin activity (group A, 3.7 ± 2.1 ng/ml/h; group B, 5.6 ± 0.8 ng/ml/h; p <0.05; control value 0.3-5.3 ng/ml/h). For ANP, statistically significant differences were present at one month after surgery (group A, 36.3 ± 5.1 pg/ml; group B, 62.9 ± 9.2 pg/ml; p <0.005; control value 27.3-37.2 pg/ml). On echocardiography, the ejection fraction, aortic valve gradient, EOAI and left ventricular mass index (LVMI) were assessed. A statistically significant difference was identified for the LVMI at 12 months postoperatively (group A, 216 ± 13 g/m^2; group B, 240 ± 18 g/m^2; p <0.05). In terms of other parameters both groups were similar.**

Conclusion: **The implantation of an aortic valve prosthesis affects the hemodynamics of the entire circulatory system, and thus the activity of natriuretic systems. Whilst stentless valves allowed much more rapid normalization of circulatory system hemodynamics (one month), no difference compared to preoperative was identified after six months. Natriuretic peptides appear to provide more sensitive (long-term) but less specific (short-term) assessment of circulatory system behavior than echocardiography.**

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Ever since the time of the first heart valve operations, cardiac surgeons have sought the ideal equivalent for the native human heart valve. The desired prosthesis should be permanent, non-thrombogenic, chemically inert, easy to implant, silent, available, cheap, have minimal technical variability, no patient discomfort, and a low risk of developing endocarditis, as well as hemodynamics equivalent to those of the healthy human native valve.

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Since the introduction of stentless bioprosthesis by David and colleagues in 1987 (1), no clear data have been provided to prove the superiority of stentless valves over their stented counterparts (2).

Several non-randomized series were reported with stentless valves placed in the aortic position, and these demonstrated better hemodynamics, especially in small aortic roots of 19 to 21 mm. Recently, however, other reports have suggested a less important role for the effective orifice area index (EOAI) and aortic valve (AV) gradient or even left ventricular mass index (LVMI) regression when describing the hemodynamics of an implanted prosthesis and the appearance of patient-prosthesis mismatch (PPM) after surgery (3).

In an attempt to better describe these changes in the cardiovascular system, cardiologists have sought new and more accurate factors. In this respect, natriuretic

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peptides appear to be very sensitive predictors of circulatory system behavior. It is well known that the levels of these hormones increase with left ventricular failure, and that their concentrations correlate directly with cardiovascular system function (4-7).

The study aim was to evaluate the possible use of plasma atrial natriuretic peptide (ANP) and renin-angiotensin-aldosterone (RAA) system activity in cardiac surgery for assessing cardiac hemodynamics after aortic valve replacement (AVR). The different types of bioprosthesis, namely stentless and stented valves, were also compared.

Clinical material and methods

Patients

Between 2001 and 2003, a total of 354 patients underwent AVR at the Second Department of Cardiac Surgery, Silesian Medical School, Katowice, Poland.

The inclusion criteria were: an ability to provide informed consent; predominant aortic stenosis (aortic regurgitation mild or trivial) requiring AVR; good left ventricular function; well-controlled blood pressure (adequate for the patient's age); no ACE-inhibitor treatment; small aortic annulus diameter (19-23 mm) on transthoracic echocardiography (TTE); and a randomized choice of bioprosthesis.

Exclusion criteria were: no consent for trial or inability to follow up; any other heart disease than aortic stenosis requiring additional surgical procedures; additional cardiac procedure (excluding intra-aortic balloon pump; IABP) during the operation unknown preoperatively; renal failure (serum creatinine >120 mmol/l); recent stroke (within past six months); and atrial fibrillation.

Difficulties encountered in identifying patients who fulfilled these inclusion criteria (small aortic root and well-controlled blood pressure) resulted in a smaller group bordering on statistical significance.

Thirty consecutive patients who met the selected inclusion criteria were chosen and allocated at random to receive either a stentless Freestyle® valve (Medtronic, Minneapolis, MN, USA; group A; n = 15; eight females, seven males; mean age 62.1 ± 5.7 years), or a stented Mosaic® bioprosthesis (Medtronic; group B; n = 15; five females, 10 males; mean age 64.4 ± 5.7 years). Both valves were manufactured using the same biological material and manufacturing technology.

Each patient underwent examinations preoperatively and at one, six and 12 months postoperatively. In all patients the level of the RAA system and ANP activity were measured preoperatively and one and six months postoperatively. Transthoracic echocardiography (TTE) was performed preoperatively and during the follow up visits at one, six and 12 months after surgery.

There were no inter-group difference in terms of Canadian Cardiothoracic Society (CCS) and NYHA class; the predominant status was class 3 (52%) for CCS, and class III (74%) for NYHA.

All patients were in sinus rhythm, six (20%) were diabetic (three in each group), and seven were hypercholesterolemic (three group A, four group B). Five group A and eight group B patients had a family history of heart disease, while five group A patients and seven group B patients were active smokers. One group A patient had a history of chronic obstructive pulmonary disease. None of the patients had renal failure or a cardiovascular event during a six-month preoperative period.

Pure aortic stenosis was observed in 11 (73%) patients of group A and 14 (93%) of group B. Five patients (four in group A) had mixed aortic disease (trivial or mild); in all cases the type of aortic valve pathology was atherosclerotic. The demographic and preoperative risk factor data were similar in both groups (see Table I).

The study was approved by the Bio-Ethics Committee of Silesian University School of Medicine on 3rd February 2001. Informed consent was acquired from each patient included in the study.

Surgical technique

Stented valves were implanted using interrupted sutures, and stentless valves using a subcoronary tech-

Table I: Demographics characteristics and preoperative risk factors of patients.

Characteristic	Stentless valves (n = 15)	Stented valves (n = 15)
Age (years)*	62.1 ± 5.7	64.4 ± 5.7
Gender ratio (M:F)	8:7	5:10
CCS grade		
0	3	4
1	9	7
2	2	5
NYHA class		
1	3	1
2	2	5
3	10	9
Stenosis	10	11
Predominant stenosis	5	4
Diabetes	3	3
Hypercholesterolemia	3	4
Family history	5	8
COPD	1	-
Smoker	5	7

*Values are mean ± SD.
COPD: Chronic obstructive pulmonary disease.

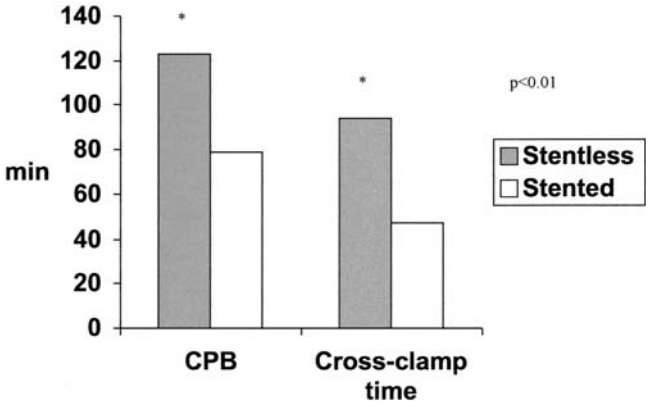

Figure 1: Cardiopulmonary bypass (CPB) and cross-clamp times for stentless and stented valve groups.

nique with interrupted sutures on the annular level and continuous in the distal layer. With regard to valve size, four patients received 19-mm valves (three Freestyle valves, one Mosaic valve). All other patients received a 21-mm prosthesis.

The mean cardiopulmonary bypass (CPB) time was 94.7 ± 19.9 min (range: 54 to 123 min) for stented valves, and 123.3 ± 16.1 min (range: 92 to 145 min) for stentless valves ($p < 0.01$). Likewise, the mean cross-clamp time was less for stented valves (47.2 ± 17 min) than for stentless valves (79.4 ± 13.1 min) (Fig. 1).

All surgical procedures were elective, with cold blood antegrade cardioplegia being used in 93.3% of cases. In two patients retrograde cardioplegia was added for myocardial protection at the surgeon's discretion.

Follow up

Clinical, operative, and follow up data were recorded prospectively on a computerized database. All patients were examined as outpatients at one and six months, and at one year postoperatively. Echocardiography was performed at each outpatient visit, whereby the aortic valve performance was assessed in terms of its effective orifice area and mean and peak pressure valve gradients. The LVMI was also measured.

The level of the RAA system and ANP activity were measured preoperatively and at one and six months postoperatively in all patients. Plasma renin activity was assessed by radioimmunoassay, in addition to levels of aldosterone and atrial natriuretic factor.

All patients were admitted to the hospital outpatient clinic early in the morning, when all basic blood investigations (full blood count, urea, creatinine, Na, K) were undertaken and 24-h urine collection initiated. Blood samples were taken and blood pressure monitored at 2 h after admission, the patients having remained in the supine position for 30 min before blood sampling.

The total follow up was 12 months and 100% complete.

Natriuretic hormone assessment

All blood testing was conducted at the Department of Nephrology, Endocrinology and Metabolic Diseases of Silesian University School of Medicine. Arterial blood samples were collected into EDTA-treated 10-ml tubes and immediately centrifuged (4ºC) to separate the plasma, which was removed and preserved at -70°C.

Radioimmunoassay analyses of ANP, aldosterone and renin were performed on at least 40 arterial blood samples. ANP was extracted from samples using solid-phase extraction (Sep-Pak, Waters, Milford, MA, USA) and assessed with polyclonal antiserum (Peninsula Laboratories, Inc.). Aldosterone and renin were assayed using a radioimmunoassay kit (Amersham, Pharmacia Biotech).

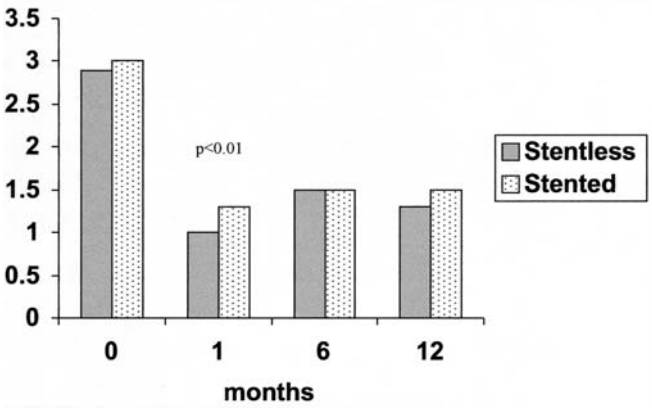

Figure 2: Preoperative and postoperative NYHA functional classes for stentless and stented valve groups.

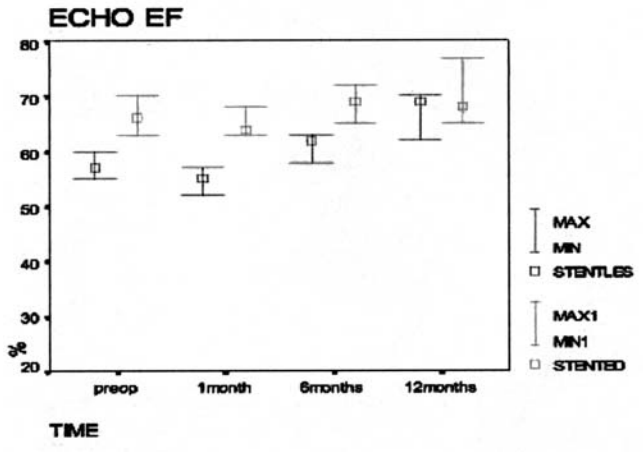

Figure 3: Preoperative and postoperative echocardiography: Ejection fraction (EF) for stentless and stented valve groups.

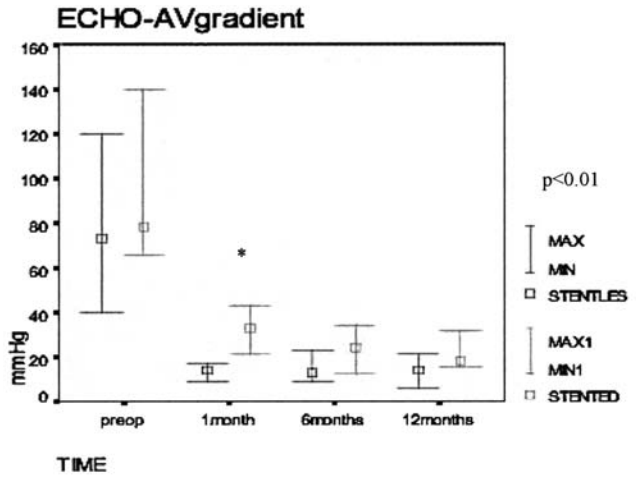

Figure 4: Preoperative and postoperative echocardiography: Aortic valve (AV) gradient across the aortic valve for stentless and stented valve groups.

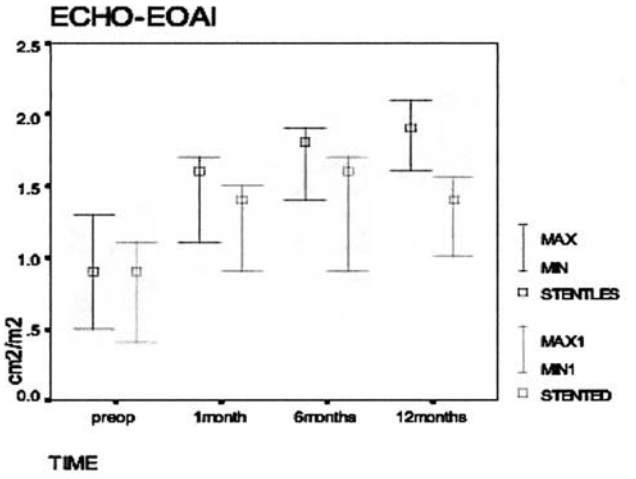

Figure 5: Preoperative and postoperative echocardiography: Effective orifice area index (EOAI) of aortic valve for stentless and stented valve groups.

Statistical analysis?

Statistical analyses were performed using SPSS version 10.0 (SPSS for Windows; SPSS Inc, Chicago, IL, USA) software. Mean values (± SD) were calculated for continuous variables. Inter-group comparisons were made using the Mann-Whitney *U*-test; a p-value <0.05 was considered to be statistically significant. Significant differences between preoperative and postoperative values in the groups were analyzed using the Wilcoxon test; again, a p-value <0.05 was considered to be statistically significant.

Results

There were no one-year mortalities in either group. Two patients from group A required IABP support immediately after surgery due to low cardiac output syndrome, two patients (one in each group) had a stroke (from which they fully recovered), and permanent pacemaker implantation was required for one patient in group A, who developed full heart block after surgery.

Paroxysmal atrial fibrillation was observed in six patients (20%) of group A and in four (13%) of group B. There was no significant difference between the groups in terms of chest and wound infections or requirement for postoperative blood transfusions.

Clinical outcome

A statistically significant reduction (p <0.01) was identified in NYHA class, with preoperative values (3.2 ± 0.3 for group A, 2.9 ± 0.4 for group B) being reduced to 1.0 ± 0.7 and 1.3 ± 0.4 respectively at one month after surgery, and to 1.3 ± 0.5 and 1.2 ± 0.6 respectively at 12 months. No significant differences were identified between the groups, however (Fig. 2).

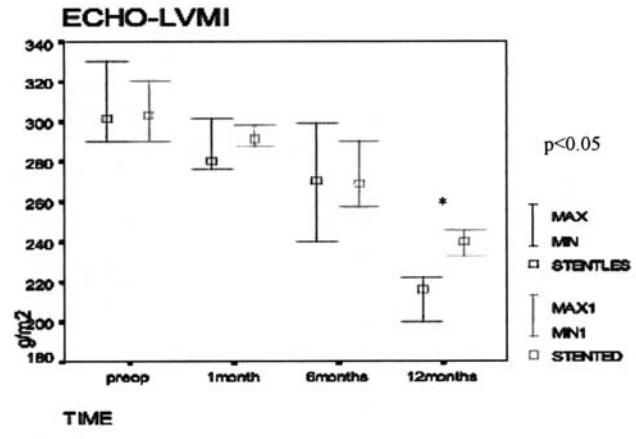

Figure 6: Preoperative and postoperative echocardiography: Left ventricular mass index (LVMI) for stentless and stented valve groups.

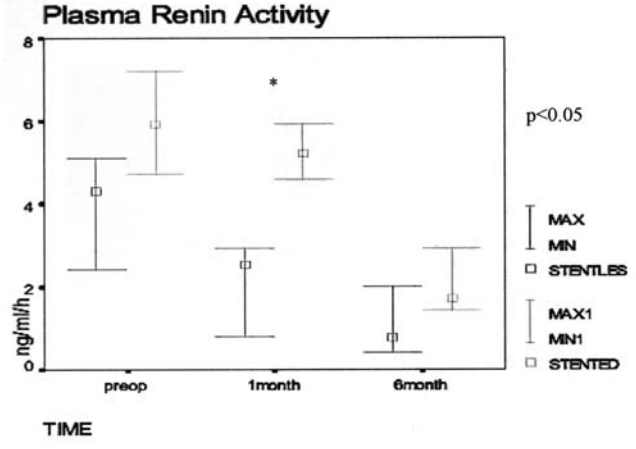

Figure 7: Preoperative and postoperative plasma renin activity for stentless and stented valve groups. Control value: 0.3-5.3 ng/ml/h.

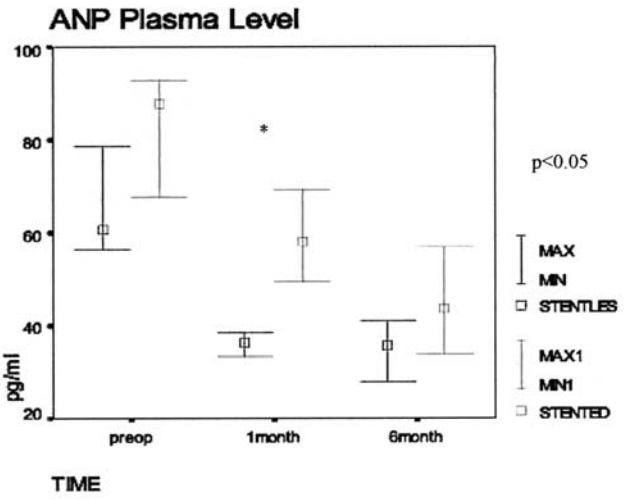

Figure 8: Preoperative and postoperative plasma levels of atrial natriuretic peptide (ANP) for stentless and stented valve groups. Control value: 27.3-37.2 pg/ml.

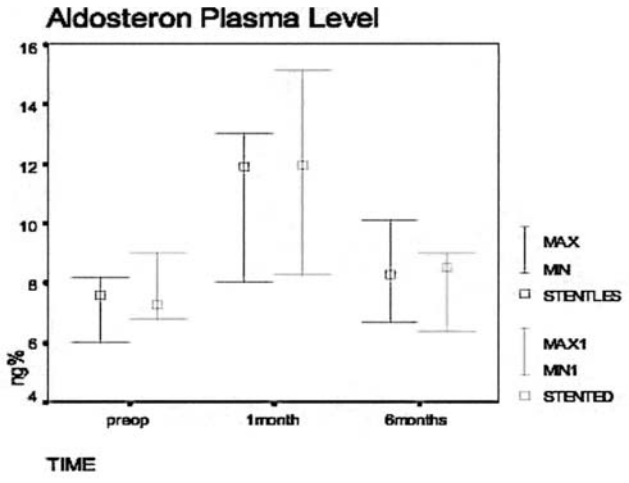

Figure 9: Preoperative and postoperative plasma levels of aldosterone for stentless and stented valve groups. Control value: <9.8 ng%.

Echocardiography

There was no significant inter-group difference in ejection fraction either before or after surgery (57 ± 3% for group A, 66 ± 2% for group B) (Fig. 3). The mean AV gradient was changed significantly after surgery, though there was no statistical difference between the stentless and stented valve groups (Fig. 4; Table II).

The EOAI was low 0.9 ± 0.5 cm^2/m^2 in all patients preoperatively, but was increased after surgery. After 12 months, no significant difference was found between EOAI for group A (1.9 ± 0.2 cm^2/m^2) and group B (1.4 ± 0.1 cm^2/m^2) (Fig. 5; Table II).

A statistical difference was also apparent between groups ($p < 0.05$) in terms of LVMI at 12 months after surgery (216 ± 13 and 240 ± 18 g/m^2 in groups A and B, respectively) that was not observed at echocardiography before surgery, nor at one and six months after surgery. There was a significant reduction in LVMI in both groups compared to the preoperative situation, and the remodeling process continued until 12 months after AVR (Fig. 6; Table II).

ANP and RAA assessment

There was no significant inter-group difference in terms of plasma ANP level and RAA system activity before surgery. The ANP plasma level was significantly elevated compared to controls (group A 70.7 ± 10.1; group B 82.7 ± 11.3; control 27.3-37.2 pg/ml) (Fig. 7; Table III).

Renin plasma activity was significantly lower at one month after surgery, there being a statistically significant difference between groups A and B (3.7 ± 2.1 and

Table II: Echocardiography findings.

Parameter/ Group	Time			
	Preoperative	1 month	6 months	12 months
EF (%)				
Group A	57 ± 3	55 ± 2	62 ± 3	69 ± 4
Group B	66 ± 2	64 ± 2	69 ± 3	68 ± 2
EOAI (cm^2/m^2)				
Group A	0.9 ± 0.5	1.6 ± 0.4	1.8 ± 0.2	1.9 ± 0.2
Group B	0.9 ± 0.3	1.4 ± 0.2	1.6 ± 0.4	1.4 ± 0.1
AV gradient (mmHg)				
Group A	73 ± 33	19 ± 8	13 ± 9	15 ± 4
Group B	78 ± 35	39 ± 7	14 ± 4	18 ± 5
LVMI (g/m^2)				
Group A	301 ± 80	280 ± 34	270 ± 45	216 ± 13
Group B	303 ± 76	291 ± 44	269 ± 55	240 ± 18

Values are mean ± SD.
AV: Aortic valve; EF: Ejection fraction; EOAI: Effective orifice area index; LVMI: Left ventricular mass index.

Table III: Atrial natriuretic peptide (ANP) plasma levels and renin-angiotensin-aldosterone (RAA) system activity.

Parameter/ Group	Time		
	Preoperative	1 month	6 months
Renin (ng/ml/h)			
Group A	4.1 ± 1.5	3.7 ± 2.1	0.7 ± 0.5
Group B	5.8 ± 1.1	5.6 ± 0.8	1.77 ± 0.9
Aldosterone (ng%)			
Group A	7.58 ± 1.2	11.89 ± 3.0	8.29 ± 3.3
Group B	7.28 ± 1.0	11.95 ± 2.5	8.5 ± 2.1
ANP (pg/ml)			
Group A	70.7 ± 10.1	36.3 ± 5.1	35.6 ± 6.6
Group B	82.7 ± 11.3	62.9 ± 9.2	53.3 ± 12.4

Values are mean ± SD.

5.6 ± 0.8 ng/ml/h, respectively; $p < 0.05$). However, similar renin levels were found in both groups at six months after surgery (0.7 ± 0.5 and 1.8 ± 0.9 ng/ml/h, respectively) (Fig. 7; Table III).

A similar behavior of ANP plasma levels was detected, with a significant difference being detected at one month after AVR (36.3 ± 5.1 versus 62.9 ± 9.2 pg/ml; $p < 0.05$), but no difference after six months (35.6 ± 6.6 versus 53.3 ± 12.4 pg/ml). However, plasma ANP levels in group B were still elevated compared to controls at six months after surgery (Fig. 8; Table III).

No differences were detected in aldosterone activity preoperatively and during the follow up period (Fig. 9).

Discussion

Although PPM is a widely recognized problem following aortic surgery, there remains no clear consensus between its definition and EOAI or clinical outcome. For example, some patients with moderate PPM (EOAI <0.85 cm^2/m^2) show no symptoms related to aortic stenosis and/or PPM, whereas others may present with symptomatic PPM but without any significant reduction in EOAI (8,9).

The aims of the present study were to identify a new means of assessing the cardiovascular system, including the hemodynamics of the implanted bioprosthesis, and to compare stented and stentless valves. Recently, new - albeit unconvincing - results have been obtained from randomized and non-randomized trials in which cardiac magnetic resonance imaging (MRI) and echocardiography were used (10). Indeed, this lack of data from previous studies was the main reason for the present to seek an alternative approach for assessing patients with stentless or stented valves.

Although stentless and stented bioprostheses are - in principle - identical, stentless valves permit the implantation of prostheses with a larger geometric effective area into an individual annulus (13), and for this reason it has been suggested that stentless valves might offer an improved hemodynamic performance (11) and survival (12) over their stented counterparts.

The use of natriuretic peptides to assess the cardiovascular system appears attractive in terms of their greater sensitivity to hemodynamic parameters associated with cardiac function. Indeed, ANP levels may serve as a surrogate marker for other cumbersome and expensive test procedures, including echocardiography to determine left ventricular function, pulmonary capillary wedge pressure, and cardiac MRI. ANP is produced by the atrium and implicated in the homeostasis of blood pressure and body fluids. The biological effects, including natriuresis, vasodilation and inhibition of renin and aldosterone secretion (14,15) are stimulated by increases in the atrial and ventricular pressures of the failing heart (16).

The RAA system not only controls the blood pressure but is also involved in the mechanisms of cardiac hemodynamics, with changes in natriuretic peptide levels having been shown to be directly related to disturbances of heart function and blood flow. Chello et al. (17) suggested that ANP plasma levels might be used routinely to support echocardiography in detecting the recovery of left ventricular function after coronary surgery. Similarly, in patients presented to the emergency department with acute dyspnea, plasma ANP levels were shown to correlate directly with the patients' NYHA classification (18).

In the present study, ANP and renin activity levels decreased more rapidly in the stentless valve group, demonstrating a significant difference at one month after surgery, though this effect did not persist. It is possible that stentless valves might be responsible for better hemodynamics in patients with a small aortic root during the early postoperative period, and recent reports appear to confirm these findings. However, no difference could be detected between stentless and stented valves in terms of echocardiographic findings

and hormone levels at six months after surgery, though this may have been related to an improved left ventricular function due to a reduction in heart mass. This process is known to be better observed in patients with left ventricular hypertrophy (LVH) and a LVMI >280 g/m^2 (12). However, whilst all of the present patients had LVH, changes in hormone levels were observed prior to echocardiographic changes.

Among the present patients, two who received stentless valves required IABP support shortly after surgery; this was considered due to postoperative low-cardiac output syndrome as a result of the longer CPB time (due to difficult prosthesis implantation). Postoperatively, there were no signs of myocardial infarction, on the basis of either electrocardiographic changes or elevated serum troponin levels. Although IABP support was withdrawn within 24 h of surgery, it is believed that the introduction of IABP, inotrope use and vascular volume changes during intensive postoperative treatment would not affect the activity of natriuretic peptides for months after surgery. The CPB times appeared not to influence ANP and the RAA system at one month after surgery.

Study limitations

The present study suffered two main limitations, namely the preselection of patients and small group sizes, both of which may have adversely affected the study outcome.

In conclusion, following AVR, plasma ANP levels and RAA system activity were seen initially to decrease more rapidly in patients receiving stentless valves, though after several months no such difference could be detected. An extended CPB did not appear to affect plasma ANP levels for one month after surgery. Whilst it may be possible to use plasma natriuretic peptides and the RAA system as an index of left ventricular function and hemodynamics, such an approach would be very costly and hence unavailable to everyday practice.

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Meeting discussion

DR. PETER SKARSGARD (Vancouver, Canada): If I understand your data correctly, there was no real difference in the AV gradients of the two groups receiving either a stented or stentless valve.

DR. ADAM SZAFRANEK (Katowice, Poland): We found a difference at one month after surgery, but it then disappeared.

DR. SKARSGARD: And there was no difference in left ventricular mass regression?

DR. SZAFRANEK: The first time that any difference appeared between the stentless and stented valve groups was at 12 months after surgery. At one month and six months there was no difference.

DR. SKARSGARD: Why do you think you found differences in the ANP and plasma renin activity?

DR. SZAFRANEK: The ANP and renin-angiotensin-aldosterone system are very sensitive, and perhaps this is what we observed in the gradient and left ventricular mass index reduction. The difference was seen only at an early stage, when we were assessing the natriuretic peptides. Unfortunately, we did not perform more echocardiograms. The difference in left ventricular mass index may disappear in the next six months. The natriuretic peptides are very sensitive - perhaps we saw the changes in left ventricular mass and in the cardiovascular system in this way, before we could see it by echocardiography.

DR. SKARSGARD: Did most of your patients have good ventricular function?

DR. SZAFRANEK: Yes - that was one of the inclusion criteria.

DR. SKARSGARD: Were there some patients who had poor ventricular function, so that you investigated their ANP and renin activity separately?

DR. SZAFRANEK: The inclusion criterion was patients with good left ventricular function, with an ejection fraction above 50%. The ANP and natriuretic peptides are affected immediately if the left ventricular function is not good. We tried to exclude that situation - which was why we could only recruit 15 patients to the group.

DR. DENNIS MODRY (Edmonton, Canada): Two questions come to mind. It seemed that both your stented and stentless valves were basically the same size - 19 or 21 mm. Is that correct?

DR. SZAFRANEK: Two more patients received a 19-mm stentless valve than a stented valve.

DR. MODRY: That is really surprising - I am wondering slightly about your technique. Did you actually efface the annulus when you put the stentless valves in?

DR. SZAFRANEK: We used a single suture, interrupted.

DR. MODRY: But did you remove totally the annulus?

DR. SZAFRANEK: No.

DR. MODRY: Because I think that does make a difference. We do remove it, and you can usually upsize by one or two valve sizes with a stentless compared to a stented valve. That might have made a difference in your study.